American Journal of Medical Genetics 66:239–240 (1996)

Letter to the Editor

Ehlers-Danlos Syndrome Type VIII and Leukodystrophy

To the Editor:

Ehlers-Danlos syndrome type VIII (EDS VIII) is a rare disorder of unknown cause inherited in an autosomal dominant mode. Specific alterations in the synthesis or secretion of collagens I and III, or ultrastructural abnormalities of skin fibroblasts and extracellular matrix, have not been demonstrated [Dyne et al., 1993]. The collagen bundle architecture appears normal [Hollister, 1982]. Diagnosis is based on clinical findings including early periodontal disease, ecchymotic pretibial lesions, minimal bruising, and premature aging [Stewart et al., 1977; Linch and Acton, 1979; Steinmann et al., 1993]. We describe a case of EDS VIII with additional cerebral involvement.

This 37-year-old woman is the second of three children born to non-consanguineous parents. Her father did not have premature loss of teeth but rather delayed healing of superficial wounds with cigarette-paper skin over the anterior tibial ridges. Her mother and two brothers were healthy. The patient noticed ecchymoses following slight trauma since age 8 years, but no episodes of severe or prolonged bleeding.

After age 10 years, the alveolar ridges of the mandible degenerated progressively with loss of all teeth. At 15 years she also lost all maxillary teeth except two. After puberty, she complained of severe headache and several episodes of drop-attacks without loss of consciousness or other neurologic deficits. Since age 20 years repeated swelling of fingers and toes occurred independent of menstruation; she suffered from hypermenorrhoe. Her body measurements were normal: height 165 cm, weight 70 kg, and head circumference 57 cm (all 50th–75th centile). Her face gave the impression of premature aging. Gingival recession and gingivitis were present. A mottled brown skin rash was distributed over the trunk. The skin over the tibial crest was extremely thin and brownish. Hypermobility of joints, hyperextensibility of skin, and contractures were absent. The neurological findings were normal, including intellectual performance.

Laboratory evaluation including normal alkaline phosphatase and urinary phospho-ethanolamine excretion excluded hypophosphatasia which may also lead to premature loss of teeth. Bleeding time, activated clot time, prothrombin time, activated partial thromboplastin time, and factor VIII were within normal range. Cerebrospinal fluid contained 1 cell/μl, normal protein content, but no local immunoglobulin production or oligoclonal bands.

Cultured skin fibroblasts synthesized and secreted collagens I, III, and V in normal amounts and proportions. The electrophoretic mobility of collagen α-chains and their precursors was normal on SDS-polyacrylamide [Steinmann et al., 1984].

Evoked potentials and EEG were normal. Repeated cranial MRI showed confluent, symmetric periventricular white matter hyperintensities (Fig. 1).

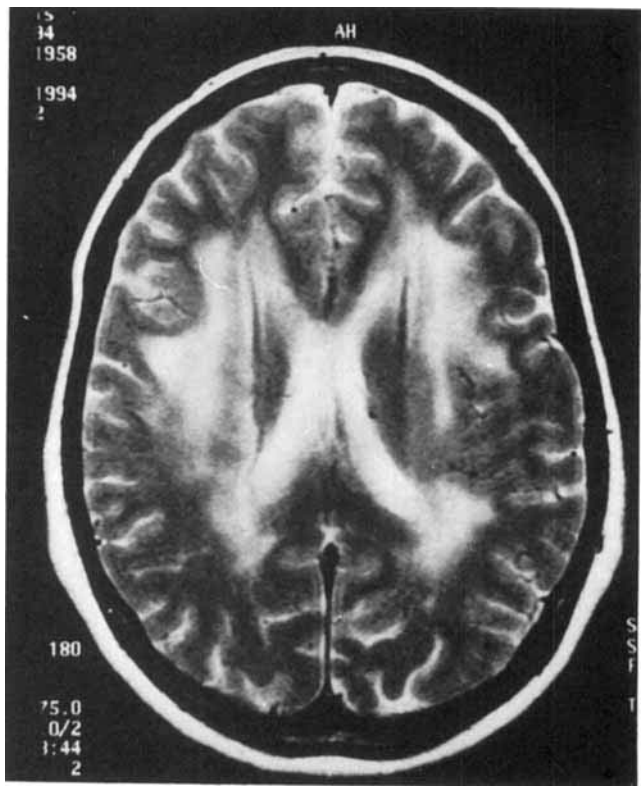

Fig. 1. Cranial MR-imaging shows confluent, symmetric periventricular white matter hyperintensities on PD and T2-weighted studies and a slightly hypointensive signal relative to adjacent brain on T1-weighted studies in the same regions. Subcortical U-fibres were spared. No abnormal enhancement occurred after administration of a paramagnetic agent. Cortex and basal ganglia appeared to be normal in signal and morphology. No ventricular enlargement or mass effect were present.

Received for publication January 22, 1996; revision received March 4, 1996.

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Clinical findings in our patient are compatible with the diagnosis EDS VIII [Linch and Acton, 1979; Steinmann et al., 1993]. Other reasons for premature loss of teeth such as hypophosphatasia and EDS type IV were excluded biochemically [Richards et al., 1992, 1993]. In addition to the characteristic clinical findings of EDS VIII, our patient had headaches, repeated drop attacks and diffuse white matter lesions of unknown origin that did not change during 5 years of observation. Edema is unlikely because there was no mass effect. Similar signal changes are seen in a variety of other diseases. Multiple sclerosis is excluded on the basis of normal CSF and electrophysiological examinations. Ischemic encephalopathy typically results in watershed infarction and bilateral selective neuronal necrosis within the basal ganglia, brainstem nuclei, and cerebellum. In microangiopathic atherosclerosis T1-weighted images often are normal or show lacunar infarctions. Noninfectious vasculitides usually cause a pattern of multifocal signal changes. Thus, the pathogenesis of the leukodystrophy-like MRI changes remains unknown. Further MRI and postmortem studies are needed to investigate a possible cerebral involvement in EDS VIII.

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